Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/040241

International filing date: 02 December 2004 (02.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/536,302
Filing date: 14 January 2004 (14.01.2004)

Date of receipt at the International Bureau: 26 January 2005 (26.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

1272400

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 11, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/536,302*
FILING DATE: *January 14, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US04/40241*

Certified By

Jon W Dudas

Under Secretary
of Commerce for Intellectual Property
and Acting Director of the
Unites States Patent and Trademark Office

PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 010320070 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Gary Lee	CANTRELL	Troy, Illinios USA

Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

TWO PHASE METHOD FOR THE SYNTHESIS OF SELECTED PYRAZOLOPYRIMIDINES

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ Customer Number: 24289

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 30 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☐ Other (specify)

☐ Application Date Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 13-1160

☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Jeffrey S. Boone

Date January 13, 2004

REGISTRATION NO. 29,284 *(if appropriate)*

Docket Number: 1675.P US

TELEPHONE 314-654-8955

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PROVISIONAL APPLICATION COVER SHEET
Additional Page

PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Docket Number 1675.P US

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Frank William	MOSER	Arnold, Missouri USA
Robert Edward	HALVACHS	Belleville, Illinois USA

Number 2 of 2

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

TWO-PHASE METHOD FOR THE SYNTHESIS OF SELECTED PYRAZOLOPYRIMIDINES

FIELD OF THE INVENTION

[0001] The present invention relates to a two-phase method for the synthesis of selected pyrazolopyrimidines and relates more specifically to an improved method for the synthesis of N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide.

BACKGROUND OF THE INVENTION

[0002] Substituted pyrazolopyrimidines are known as actives for anxiolytic, anticonvulsant, antiepileptic, sedative-hypnotic and skeletal muscle relaxant agents. Illustrative substituted pyrazolopyrimidines include N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide, (hereinafter zaleplon, discussed below), and N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1, 5-a]-pyrimidin-7-yl}phenyl)acetamide (herein after Indiplon™, disclosed in U.S. Patent No. 6,399,621).

[0003] Zaleplon is known as having anxiolytic, antiepileptic, sedative and hypnotic properties. The U.S. F.D.A. has approved zaleplon for use for short-term treatment of insomnia. The prior art discloses a method for preparing zaleplon in U.S. Patent No. 4,626,538, wherein N-(3-acetylphenyl)ethanamide is condensed with dimethylformamide dimethyl acetal to form N-[3-[3-(dimethylamine)-1-oxo-2-propenyl)]phenyl]acetamide. The primary amide of the acetamide is then alkylated with ethyl iodide to form N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide. The ethylacetamide is then condensed with 3-amino-4-cyanopyrazole in refluxing glacial acetic acid for eight hours until the conversion to zaleplon is substantially complete.

[0004] U.S. Pat. 5,714,607 discloses an improvement over the '538 process for producing zaleplon. It is claimed in the '607 patent that improved yield and purity can be obtained at a faster rate if the final step of the '538 process is modified by adding water to the acetic acid solvent at about 10% to about 85% (v/v). The improved conditions are stated to shorten the reaction time from 3-3.5 to 1-3.5 hours. The improved reaction is said to result in yields ranging from 81.7-90 % with purity ranging from 98.77 to 99.4 % according to HPLC analysis.

[0005] WO O2/100828 A2 discloses a further improvement in the '538 process by reacting the same intermediates, N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide and 3-amino-4-cyanopyrazole, in a liquid medium of water and a water-miscible organic compound under acidic conditions. Although the reaction is claimed to proceed through an imine intermediate that was prone to precipitate from water, the imine intermediate remained dissolved in the reaction media. It is stated in the '828 patent that the process proceeds rapidly at ambient temperature to produce zaleplon with a 91-97 % yield having a purity ranging from 98.7 to 99.5 % according the HPLC analysis. The method minimized the formation of a regioisomer by-product, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)phenyl]-N-ethylacetamide which is favored under excess acid conditions.

[0006] It is therefore desirable to have an improved process for the preparation of substituted pyrazolopyrimidines that results in near quantitative conversion after a few hours at ambient temperature.

SUMMARY OF THE INVENTION

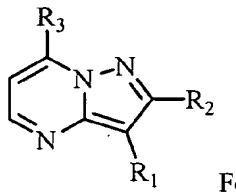
[0007] An aspect of the present invention is to provide an improved method of making a substituted pyrazolopyrimidine compound. The method comprises reacting an aminopyrazole compound or a salt thereof with a substituted 1-oxo-2-propenyl-compound or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.

[0008] This is merely an illustrative aspect of the present invention and should not be deemed an all-inclusive listing of the aspects associated with the present invention. These other aspects will become apparent to those skilled in the art in light of the following disclosure.

DETAILED DESCRIPTION

[0009] There is provided a two-phase synthesis of substituted pyrazolopyrimidines resulting in near quantitative conversion at moderate temperatures.

[0010] The substituted pyrazolopyrimidines, or pharmaceutically acceptable salts thereof, of the present invention are represented by Formula I:



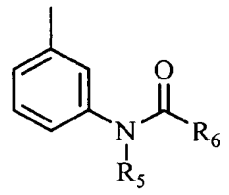
[0011] Formula I

[0012] wherein R_1 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, formyl, carboxyl, cyano, hydroxymethyl, N-hydroxyformimidoyl and R_4CO- with R_4 selected from the group consisting of hydrogen; alkyl(C_1-C_6); alkoxy(C_1-C_6); unsubstituted phenyl; phenyl mono- or disubstituted by halogen, alkyl(C_1 –C_3) or alkoxy(C_1 –C_3); phenyl (C_1 –C_3), phenyl substituted by trifluoromethyl, alkylthio(C_1 –C_3), alkylamino(C_1 –C_3), dialkylamino(C_1 –C_3), methylenedioxy, alkylsulfonyl(C_1 –C_3) or alkanoylamino(C_1 –C_3); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl, wherein the substituents are selected from one or two of the groups consisting of halogen, alkyl(C_1 –C_3) and alkoxy(C_1 –C_3);

[0013] R_2 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, cyano, cyanomethyl, carbamoyl and alkyl (C_1 –C_3); and

[0014] R_3 is selected from the group consisting of phenyl; o-trifluoromethylphenyl; m-trifluoromethylphenyl; m-methoxyphenyl, pyridyl, pyridyl N-oxide, thienyl, furanyl, and

substituted phenyl wherein one or more of the positions is substituted by a group represented by



Formula II

[0015] Formula II

[0016] wherein R_5 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl, cycloalkyl(C_3-C_6)methyl, -CH_2OCH_3, –$CH_2CH_2OCH_3$,–CH_2CH_2OH, –$CH_2CHOHCH_2OH$, and –$[CH_2CH_2O]_{n=10\text{-}120;}$ and

[0017] R_6 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_3), -N-dialkyl(C_1-C_3), -(CH_2)nO-alkyl(C_1-C_3), -$(CH_2)_n$NH-alkyl(C_1-C_3) and -$(CH_2)_n$N-dialkyl(C_1-C_3), where n is an integer 1 to 3 inclusive.

[0018] Illustrative compounds that may be synthesized by the present method include but are not limited to:

[0019] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylpropanamide;

[0020] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide;

[0021] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-propylacetamide;

[0022] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(polyethyleneglycol)acetamide;

[0023] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(methoxyethyl)acetamide;

[0024] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(hydroxyethyl)acetamide;

[0025] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1',2'-propanediol)acetamide;

[0026] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1'-propanol)acetamide;

[0027] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(2'-propanol)acetamide;

[0028] [3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

[0029] 7-[3-[(methoxycarbonyl)methylamino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester;

[0030] [3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester;

[0031] ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester;

[0032] [3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

[0033] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

[0034] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

[0035] N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide;

[0036] 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

[0037] 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0038] 2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0039] 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

[0040] 2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

[0041] 7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

[0042] 7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0043] 6-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0044] 3-bromo-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

[0045] 3-chloro-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

[0046] 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine, pyridine-1-oxide;

[0047] 2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0048] 2,6-dimethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0049] 2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

[0050] N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide;

[0051] N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclopropanecarboxamide;

[0052] [3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

[0053] N-methyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-cyclopropanecarboxamide;

[0054] [3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

[0055] [3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

[0056] N-2-propenyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide;

[0057] ethyl[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]carbamic acid, ethyl ester;

[0058] N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

[0059] N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

[0060] N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1, 5-a]-pyrimidin-7-yl}phenyl)acetamide;

[0061] 7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0062] ethyl 7 (α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

[0063] methyl 7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidin-3-yl ketone;

[0064] 7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxaldehyde oxime;

[0065] 7-(m-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0066] 3-(methoxymethyl)-7-(α,α,α–trifluoro-m-tolyl)pyrazolo-[1 ,5-a]pyrimidine;

[0067] 3-bromo-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

[0068] 2-cyano-7(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0069] 3-cyano-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]-pyrimidine-2-acetonitrile;

[0070] 3-methyl-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

[0071] ethyl 7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

[0072] ethyl 7-(3,4-xylyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

[0073] ethyl 7-(p-ethylphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

[0074] ethyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

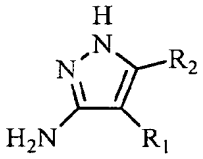
[0075] 7-(m-fluorophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

[0076] 5-phenylpyrazolo[1,5-a]pyrimidine; and

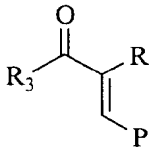
[0077] 5-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine.

[0078] The substituted pyrazolopyrimidines according to Formula I are synthesized by the reaction of a pyrazole compound according the Formula III or a salt thereof with an a substituted 1-oxo-2-propenyl-arene(heterocycle) compound according to Formula IV or a salt thereof, both illustrated below:

[0079] Formula III



Formula IV

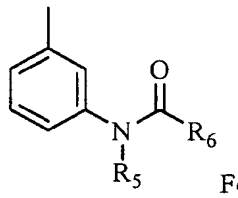


[0080] wherein R_1 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, formyl, carboxyl, cyano, hydroxymethyl, N-hydroxyformimidoyl and R_4CO-, wherein R_4 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkoxy(C_1-C_6), unsubstituted

phenyl; phenyl mono- or disubstituted halogen, alkyl(C_1 –C_3) or alkoxy(C_1 –C_3); phenyl (C_1 – C_3), phenyl substituted by trifluoromethyl, alkylthio(C_1 –C_3), alkylamino(C_1 –C_3), dialkylamino(C_1 –C_3), methylenedioxy, alkylsulfonyl(C_1 –C_3) or alkanoylamino(C_1 –C_3); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl, wherein the substituents are selected from one or two of the groups consisting of halogen, alkyl(C_1 –C_3) and alkoxy(C_1 –C_3);

[0081] R_2 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, cyano, cyanomethyl, carbamoyl or alkyl (C_1 –C_3); and

[0082] wherein R_3 is a group such as phenyl; o-trifluoromethylphenyl; m-trifluoromethylphenyl; m-methoxyphenyl, substituted pyridyl, pyridyl N-oxide, thienyl, furanyl or represented by Formula II



[0083] Formula II

[0084] wherein R_5 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl, cycloalkyl(C_3-C_6)methyl, -CH_2OCH_3, –$CH_2CH_2OCH_3$,–CH_2CH_2OH, – $CH_2CHOHCH_2OH$, and –$[CH_2CH_2O]_{n=10\text{-}120}$;

[0085] R_6 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_3), -N-dialkyl(C_1-C_3), -(CH$_2$)nO-alkyl(C_1-C_3), -$(CH_2)_n$NH-alkyl(C_1-C_3) and -$(CH_2)_n$N-dialkyl(C_1-C_3), where n is an integer 1 to 3 inclusive;

[0086] P is selected from the group consisting of –OAc, -OR, -SR and –NR'R; and

[0087] R and R' are selected from the group consisting of hydrogen, alkyl(C_1-C_6) and cyclic alkyl.

[0088] The reaction of Formula III or a salt thereof with Formula IV or a salt thereof takes place under acidic conditions in a reaction medium comprising a two-phase mixture of an aqueous solution and a water-immiscible organic liquid at about room temperature.

[0089] The reaction medium may contain a phase-transfer agent to facilitate the reaction rate. Suitable phase-transfer agents include but are not limited to the following: Aliquat® 336, ALKANOL®s, Polyethylene(PEG) esters and diesters, polypropylene glycol (PPG) and PEG-PPG copolymers, tetraalkylammonium salts, tetraalkylphosphonium salts, N-alkylpyridinium salts, sodium stearate, sodium palmitate, sodium laurate. Although the reaction medium can under some circumstances form a microemulsion or emulsion, two phases that separate quickly on settling are preferred.

[0090] The aqueous solution phase includes but is not limited to water including a dissolved acid. The aqueous solution may include at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

[0091] Water-soluble salts may be added to the aqueous solution to reduce product losses to the aqueous phase. These salts may include a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

[0092] The aqueous immiscible phase may include an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and

xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

[0093] The condensation reaction in general requires one equivalent of an acid unless the acid salts of either or both of the two reactants are used, as is well known in the art. Suitable acids include mineral acids, organic acids and mixtures thereof. Acceptable mineral and organic acids may include at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

[0094] An illustrative advantage of the present invention over the prior art is that upon completion of the reaction the product is easily separated by removing the product-containing organic phase from the aqueous phase containing the remaining reactants. After conventional solvent removal and recovery, the product is usually of acceptable purity. However, the product may be crystallized from the organic phase solvent by concentrating and cooling. The method of the present invention has the advantage that problematic regioisomers are only produced in trace quantities in the environment of the reaction medium.

[0095] An illustrative use of the present invention is the production of zaleplon, wherein an analog of Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide and an analog of Formula III is 3-amino-4-cyanopyrazole. The N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide is reacted with the 3-amino-4-cyanopyrazole under acidic conditions in a reaction medium comprising a two-phase mixture of an aqueous solution and a water-immiscible organic liquid at about room temperature, according to the present invention as discussed above. An unexpectedly preferred water immiscible organic liquid is one that

includes methylethylketone, 2-butanone. It would be expected that the 3-amino-4-cyanopyrazole would be consumed by a reaction with 2-butanone to form a Schiff's base, but this is not observed when one equivalent of acid is used.

[0096] The product optionally may be crystallized from the organic phase solvent. An improvement is that in the production of zaleplon by the present invention the problematic regioisomer, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)phenyl]-N-ethylacetamide, described in the prior art above, is only formed in trace quantities in the environment of the reaction medium.

[0097] Another illustrative use of the present invention is the production of Indiplon™ wherein an analog of Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide and is reacted with an analog of Formula III, (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone under acidic conditions in a reaction medium comprising a two-phase mixture of an aqueous solution and a water-immiscible organic liquid at about room temperature, according to the present invention as discussed above. Typically, one equivalent of acid is used. The product optionally may be crystallized from the organic phase solvent.

[0098] The following examples are given for the purposes of illustration only and are not intended to be limiting of the present invention in any way.

[0099] Example 1:

[0100] N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide (1.3 g) and 3-amino-4-cyanopyrazole (0.54 g) were weighed into a 50 mL Erlenmeyer flask containing a magnetic stir bar. Water (17 mL), 2-butanone (15 mL) and 37 % HCl (0.5 mL) were added to form the two-phase mixture. The two-phase mixture was stirred vigorously at room temperature and sampled for HPLC (50 μL each phase/100 mL methanol) at 30 minutes, 60 minutes, 90 minutes and after stirring overnight. The area percents for zaleplon were 39.5 % 71.2 % 81.7 % and 100 % at the stated time intervals, respectively.

[0101] Example 2:

[0102] N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide (1.3 g), 3-amino-4-cyanopyrazole (0.54 g) were weighed into a 50 mL Erlenmeyer flask containing a magnetic stir bar. Water (17 mL), 2-butanone (17 mL) and of heptafluorobutyric acid (0.5 mL) were added to form the two phases. The two-phase mixture was stirred vigorously at room temperature and sampled for HPLC (50 μL each phase/100 mL methanol) at 30 minutes, 60 minutes, 90 minutes, and after stirring overnight. The area percents for zaleplon were 55.0 %, 77.5 %, 86.7 % and 100 % at the stated time intervals, respectively.

[0103] Example 3:

[0104] The reaction of Example 1 was repeated using (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone in place of the and N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide as reactants, wherein the product is Indiplon™.

[0105] Example 4:

[0106] Procedure to Prepare a Kilogram of Zaleplon

[0107] N-[3-(3-Dimethylamino-1-oxo-2-propenyl)phenyl]-N-ethylacetamide (1001 g, 3.85 mol), 3-amino-4-cyanopyazole (422 g, 3.90 mol), 2-butanone (5.77 L, 4.64 kg) and water (5.77 L) were added to a glass reactor equipped with temperature control, stirring and nitrogen sweep. The resulting reaction mixture was stirred at about 25-30°C until the solids were substantially dissolved. Hydrochloric acid (325 mL; 390 g) was diluted with water (1.86 L) and added in 4 equal portions over a one-hour period to the reaction mixture. The resulting reaction mixture was stirred for 1 to 2 hours at 25-35°C. The reaction mixture was then heated to boiling. Approximately 4.65 L of volatiles were taken off until the pot temperature reached 79-80°C.

[0108] Water (1.86 L) was added and the reaction mixture was cool to 25-40°C. The cooled reaction mixture was filtered. The resulting cake was washed with water (3.7 L). The remaining solids were dried at 90°C.

[0109] The crude zaleplon weighed 1073 g for a 92.5 % yield.

[0110] The crude zaleplon was combined with ethanol (5.365 L) and water (0.536 L) in a glass vessel and heated to reflux at about 80°C. The resulting mixture was filtered to remove insoluble materials and then washed with ethanol (0.1L). The filtrate was combined with the wash liquor and resuspended with stirring at 5-10°C for about one hour. The product was separated by filtration. The filtrate was washed with a 50:50 solution of ethanol and water (1 L). The solids were dried at 90°C yielding about 1 kg of zaleplon.

[0111] HPLC Results:

Sample	Assay w/w	N-Me Zal. %a	RI IMP%a	MW 520 %a
CRUDE	*	0.20	0.15	0.18
PURIFIED	101.4%	0.21	0.07	0.23

*Assay was not run.

Claims

1. A method of making a substituted pyrazolopyrimidine, the method comprising reacting a aminopyrazole compound or a salt thereof with a substituted 1-oxo-2-propenyl-compound or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-miscible organic liquid.

2. The method of claim 1 wherein the reaction mixture further includes at least one phase-transfer agent.

3. The method of claim 2 wherein the at least one phase-transfer agent includes a water-soluble salt.

4. The method of claim 3 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

5. The method of claim 1 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures, thereof.

6. The method of claim 5 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

7. The method of claim 1 wherein the aqueous phase includes water.

8. The method of claim 1 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol,

propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

9. The method of claim 1 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

10. The method of claim 1 further including extracting the pyrazolopyrimidine from the water immiscible organic liquid.

11. The method of claim 10 further included recrystallizing the extracted pyrazolopyrimidine.

12. The method of claim 1 wherein the pyrazolopyrimidine is zaleplon.

13. The method of claim 1 wherein the pyrazolopyrimidine is Indiplon™.

14. The method of claim 1 wherein the pyrazolopyrimidine is selected from the group consisting of:

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylpropanamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-propylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(polyethyleneglycol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(methoxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(hydroxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1',2'-propanediol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1'-propanol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(2'-propanol)acetamide;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

7-[3-[(methoxycarbonyl)methylamino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ether;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester;

ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester;

[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

6-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-bromo-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

3-chloro-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine, pyridine-1-oxide;

2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2,6-dimethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclopropanecarboxamide;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

N-methyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-cyclopropanecarboxamide;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-2-propenyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-acetamide;

ethyl[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]carbamic acid, ethyl ester;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1, 5-a]-pyrimidin-7-yl}phenyl)-acetamide;

7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

ethyl 7 (α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

methyl 7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidin-3-yl ketone;

7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxaldehyde oxime;

7-(m-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-(methoxymethyl)-7-(α,α,α–trifluoro-m-tolyl)pyrazolo-[1 ,5-a]pyrimidine;

3-bromo-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

2-cyano-7(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-cyano-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]-pyrimidine-2-acetonitrile;

3-methyl-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

ethyl 7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

ethyl 7-(3,4-xylyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

ethyl 7-(p-ethylphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

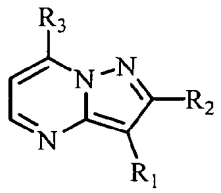
ethyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

7-(m-Fluorophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

5-Phenylpyrazolo[1,5-a]pyrimidine; and

5-(α,α,α–Trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine.

15. A method of making a substituted pyrazolopyrimidine, or pharmaceutically acceptable salt thereof, of Formula I,

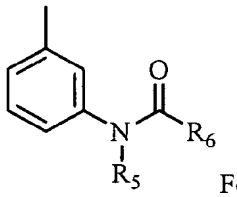


Formula I

wherein R_1 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, formyl, carboxyl, cyano, hydroxymethyl, N-hydroxyformimidoyl and R_4CO- wherein R_4 is selected from the group consisting of hydrogen; alkyl(C_1-C_6); alkoxy(C_1-C_6); unsubstituted phenyl; phenyl mono- or disubstituted by halogen, alkyl(C_1 –C_3) or alkoxy(C_1 –C_3); phenyl (C_1 –C_3), phenyl substituted by trifluoromethyl, alkylthio(C_1 – C_3), alkylamino(C_1 –C_3), dialkylamino(C_1 –C_3), methylenedioxy, alkylsulfonyl(C_1 –C_3) or alkanoylamino(C_1 –C_3); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl, wherein the substituents are selected from one or two of the groups consisting of halogen, alkyl(C_1 –C_3) and alkoxy(C_1 –C_3);

R_2 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, cyano, cyanomethyl, carbamoyl or alkyl (C_1 –C_3); and

wherein R_3 is selected from the group consisting of phenyl; o-trifluoromethylphenyl; m-trifluoromethylphenyl; m-methoxyphenyl; pyridyl; pyridyl N-oxide; thienyl; furanyl; and substituted phenyl, wherein one or more of the positions is substituted by a group represented by Formula II



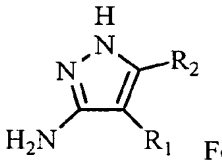
Formula II

wherein R_5 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl, cycloalkyl(C_3-C_6)methyl, -CH_2OCH_3, –$CH_2CH_2OCH_3$,–CH_2CH_2OH, –$CH_2CHOHCH_2OH$, and –$[CH_2CH_2O]_{n=10\text{-}120}$; and

R_6 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_3), -N-dialkyl(C_1-C_3), -(CH_2)nO-alkyl(C_1-C_3), -$(CH_2)_n$NH-alkyl(C_1-C_3) and -$(CH_2)_n$N-dialkyl(C_1-C_3), where n is an integer 1 to 3 inclusive;

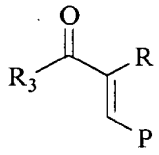
the method comprising:

reacting a compound of Formula III or a salt thereof with a compound of Formula IV or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid, wherein Formula III is



Formula III

and Formula IV is



Formula IV

P is selected from the group consisting of –Oac, -OR, -SR and –NR'R; and

R and R' are selected from the group consisting of hydrogen, alkyl(C_1-C_6) and cyclic alkyl.

16. The method of claim 15 wherein the reaction mixture further includes at least one phase transfer agent.

17. The method of claim 16 wherein the at least one phase transfer agent includes but are not limited to the following: Aliquat® 336, ALKANOL®s, Polyethylene(PEG) esters and diesters, polypropylene glycol (PPG) and PEG-PPG copolymers, tetraalkylammonium salts, tetraalkylphosphonium salts, N-alkylpyridinium salts, sodium stearate, sodium palmitate, sodium laurate.

18. The method of claim 17 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

19. The method of claim 15 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

20. The method of claim 19 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

21. The method of claim 15 wherein the aqueous phase includes water.

22. The method of claim 15 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol,

polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

23. The method of claim 15 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

24. The method of claim 15 further including extracting the compound of Formula I from the water immiscible organic liquid.

25. The method of claim 24 further included recrystallizing the extracted compound of Formula I.

26. The method of claim 15 wherein Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide, Formula III is 3-amino-4-cyanopyrazole and Formula I is zaleplon.

27. The method of claim 15 wherein Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide, Formula III is (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone and Formula I is Indiplon™.

28. The method of claim 15 wherein Formula I is selected from the group consisting of N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(hydroxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1',2'-propanediol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1'-propanol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(2'-propanol)acetamide;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

7-[3-[(methoxycarbonyl)methylamino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester;

ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester;

[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

6-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-bromo-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

3-chloro-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine, pyridine-1-oxide;

2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2,6-dimethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclopropanecarboxamide;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

N-methyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-cyclopropanecarboxamide;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-2-propenyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide;

ethyl[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]carbamic acid, ethyl ester;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1, 5-a]-pyrimidin-7-yl}phenyl)acetamide;

7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

ethyl 7 (α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

methyl 7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidin-3-yl ketone;

7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxaldehyde oxime;

7-(m-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-(methoxymethyl)-7-(α,α,α–trifluoro-m-tolyl)pyrazolo-[1 ,5-a]pyrimidine;

3-bromo-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

2-cyano-7(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-cyano-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]-pyrimidine-2-acetonitrile;

3-methyl-7-(α,α,α–trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;

ethyl 7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

ethyl 7-(3,4-xylyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

ethyl 7-(p-ethylphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

ethyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;

7-(m-Fluorophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

5-Phenylpyrazolo[1,5-a]pyrimidine; and

5-(α,α,α–Trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine.

29. A method for making zaleplon, the method comprising:

reacting N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide with 3-amino-4-cyanopyrazole under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.

30. The method of claim 29 wherein the reaction mixture further includes at least one phase transfer agent.

31. The method of claim 30 wherein the at least one phase transfer agent includes a water soluble salt.

32. The method of claim 31 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

33. The method of claim 29 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

34. The method of claim 33 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

35. The method of claim 29 wherein the aqueous phase includes water.

36. The method of claim 29 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

37. The method of claim 29 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane,

methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

38. The method of claim 29 further including extracting the zaleplon from the water immiscible organic liquid.

39. The method of claim 38 further included recrystallizing the extracted zaleplon.

40. A method for making Indiplon™, the method comprising:

reacting N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide with (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.

41. The method of claim 40 wherein the reaction mixture further includes at least one phase transfer agent.

42. The method of claim 41 wherein the at least one phase transfer agent includes a water soluble salt.

43. The method of claim 42 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

44. The method of claim 40 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

45. The method of claim 44 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

46. The method of claim 40 wherein the aqueous phase includes water.

47. The method of claim 40 wherein the aqueous phase includes at least one water miscible solvent selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof..

48. The method of claim 40 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

49. The method of claim 40 further including extracting Indiplon™ from the water immiscible organic liquid.

50. The method of claim 40 further included recrystallizing the extracted Indiplon™.

TWO-PHASE METHOD FOR THE SYNTHESIS OF SELECTED PYRAZOLOPYRIMIDINES

Abstract of Disclosure

An improved method of making a substituted pyrazolopyrimidine. The method comprises reacting a aminopyrazole compound or a salt thereof with a substituted 1-oxo-2-propenyl-arene(-heterocycle) or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid. Specific substituted pyrazolopyrimidines include N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide and N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazolo[1, 5-a]-pyrimidin-7-yl}phenyl)acetamide.